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(19) (CA) **CANADIAN PATENT** (12)

(54) MICROPARTICLE DRUG DELIVERY SYSTEM

(72) Beck, Lee R.;
Flowers, Charles E.;
Cowsar, Donald R.;
Tanwuany, Albert C.,
U.S.A.

(73) Granted to Stolle Research and Development Corporation
U.S.A.

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ABSTRACT OF THE DISCLOSURE

Antibody or antigen containing microparticles for the active or passive immunization of the internal female reproductive organs, comprising microparticles of an antigen or antibody incorporated in a matrix material which is biocompatible and biologically degradable, said microparticles capable of being transported after deposition in the vagina by the natural transport mechanism of the internal female reproductive organs across the cervix into the uterus. A contraceptive composition capable of being directly delivered to the uterus and fallopian tubes comprising microparticles of a biodegradable and biocompatible matrix material having sperm surrogate activity and containing a contraceptive agent and a transport inducing hormone which when released stimulates the transport of the microparticles across the cervix into the uterus and fallopian tubes with the proviso that the contraceptive agent and hormone are different when the contraceptive agent is a hormone.

MICROPARTICLE DRUG DELIVERY SYSTEM

BACKGROUND OF THE INVENTIONField of the Invention:

5 The present invention relates to a method for introducing therapeutic or medicinal agents into the uterus and fallopian tubes of the internal female reproductive organs.

Description of the Prior Art:

10 In the past, the methods of generally treating the internal reproductive organs of the female have included principally the oral ingestion or the injection of drugs into the patient in order to treat diseases and to regulate the female reproductive cycle. Few methods are known by which the female reproductive organs can be treated by delivery of a therapeutic agent directly to the uterus. One technique which achieves the direct delivery of a contraceptive steroid to the uterus is the progestert
15 device which is a medicated intrauterine device. The device is described in U.S. Patent No. 3,699,951 and No. 3,777,015 by Zaffaroni. The disadvantage of the insertable device is that it requires a trained physician to place the device in the uterus.
20 There exists still, therefore, a need for an improved method of delivering a contraceptive agent as well as other medicinal



agents such as antigens and antibodies which can be self-administered.

Several techniques are known by which contraceptive agents in the form of microcapsules can be introduced into the vagina, however, in these techniques transport of the microcapsules across the cervix into the uterus does not occur. For instance, U. S. Patent Nos. 3,918,452 and 3,921,636 show techniques in which a pharmaceutical agent is released from microparticles in a tampon which is placed in the vagina.

The technique shown by Zaffaroni in U. S. Patent Nos. 3,699,951 and 3,777,015 describes an intrauterine device designed to release progesterone directly into the uterus for the purpose of contraception. This device, however, is non-biodegradable and it must be placed in the uterus and removed from the uterus following use by a trained physician. Accordingly, the utility of the device is limited by the fact that it cannot be self-administered.

Early studies have been conducted to investigate the scope of possible particulate materials which will migrate across the cervix into the uterus after deposition in the vagina. Thus, it

has been shown that carbon particles from a cap containing a suspension of carbon particles, when placed over the cervix, can be recovered from the uterus after coitus (Amersbach, "Sterilitat Und Frigiditat," Muchen. Med. Wchnschr. 77: 225, 1930). J. Trapl, "Neuve Anschauung uber den Ei-und Samen-transport in den Geschlechtsteilen de Frau," Zentralbl. Gynak. 67: 547, 1943, has shown that even without the use of a cervical cap, carmine particles migrate thus demonstrating that non-motile particles other than carbon also migrate.

Still further, R. Krehbiel and H. P. Carstens, "Roentgen Rabbit", Am. J. Physiol. 125: 571, 1959, have shown that the passage of a radio-opaque oil, when placed in the vagina of a rabbit was blocked until after the vulva was stimulated, while other investigators have shown that graphite and dyes in gelatin were not transported across the cervix. The implication of the data is that the nature of the particles affects the transport process and that transport is assisted by muscular contractions. Hartman, in "How Do Sperms Get Into the Uterus?" Fertil. and Steril 8: 403, 1957, concluded that in the transport of sperm in the reproductive tract, transport occurs principally by

cooperation of the particles with the musculature of the female reproductive tract. G. M. Duncan and D. R. Kalkwarf, "Sustained Release Systems for Fertility Control," in: Human Reproduction: Conception and Contraception, edited by E. S. E. Hafez and T. N. Evans, Harper and Row, New York, 1973, have concluded from experiments that non-motile particles which are about the size of the head of the sperm migrate directionally through the cervix to the fallopian tubes. However, the article shows that progesterone containing microcapsules of cellulose acetate butyrate and of a size ranging from 5 to 1400 μm do not migrate across the cervix into the uterus, but are transported in the reverse direction. Therefore, the reference clearly suggests that microcapsules of a size greater than 5 μm will not migrate inward to the internal female reproductive organs.

SUMMARY OF THE INVENTION

Accordingly, the present invention seeks to provide a means by which medicinal and therapeutic agents can be locally administered to the vagina and transported through the cervix into the uterus to treat the internal female reproductive organs.

The present invention also seeks to provide micro-particles containing a pharmaceutical agent, which, when deposited in the vagina, can be transported across the cervix into the uterus by the natural transport mechanism of the internal reproductive organs.

Briefly, these aspects and other aspects of the present invention as hereinafter will become more readily apparent, are provided in one aspect by antigen or antibody containing microparticles for the active or passive immunization of the internal female reproductive organs, which comprise, microparticles containing an amount of antigen or antibody sufficient to elicit a response incorporated in a matrix material which is biocompatible and biologically degradable, the microparticles capable of being transported after deposition in the vagina by the natural mechanism of the internal female reproductive organs across the cervix into the uterus.

Another aspect of the invention comprehends microparticles containing contraceptive agent capable of being transported by the natural transport mechanism of the internal female reproductive organs into at least the uterus, the microparticles comprises, a cycle regulatory hormone and contraceptive agent incorporated in a biocompatible and biodegradable matrix material as microparticles which possess sperm surrogate activity with the proviso that when the contraceptive agent is a hormone, the contraceptive hormone and cycle regulatory hormones are different, the cycle regulatory hormone being capable of stimulating the natural transport mechanism after the microparticles have been deposited in the vagina.

25 BRIEF DESCRIPTION OF THE DRAWINGS

A more complete appreciation of the present invention and many of the attendant advantages thereof will be readily obtained as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings, wherein:

FIGURE 1 shows microparticles of a monolithic structure

containing a pharmaceutical agent;

FIGURE 2 shows microparticles formed of a core of pharmaceutical agent in a matrix material surrounded by a shell of matrix material;

5 FIGURE 3 shows microparticles formed of a core of pharmaceutical agent surrounded by a shell of matrix material;

FIGURE 4 shows microparticles of an onion-skin structure of alternating layers of matrix material and pharmaceutical agent;

10 FIGURE 5 shows microparticles formed of a core of one particular pharmaceutical agent surrounded by a shell of matrix material containing a second type of pharmaceutical agent;

FIGURE 6 shows monolithic microparticles of contraceptive agent and cycle regulatory hormone in a matrix material;

15 FIGURE 7 shows microparticles of a core of contraceptive agent and cycle regulatory hormone surrounded by a shell of matrix material;

FIGURE 8 shows microparticles of a core of contraceptive agent and cycle regulatory hormone in a matrix material surrounded
20 by a shell of matrix material;

FIGURE 9 shows microparticles of a core of contraceptive agent in a matrix material surrounded by a shell of cycle regulatory hormone in matrix material;

5 FIGURE 10 shows multi-layered microparticles in which contraceptive agent and cycle regulatory hormone are dispersed throughout different layers;

FIGURES 11A and 11B show the blood levels of progesterone and estradiol in baboons treated intramuscularly and intravaginally respectively with 7.87 mg of progesterone;

10 FIGURE 12 is a series of photomicrographs showing the histological appearance of baboon endometrium;

FIGURE 13 is a series of photomicrographs showing the morphology of the uterine epithelial surface of baboons;

15 FIGURES 14A and 14B show the blood levels of progesterone and estrogen in baboons treated intramuscularly and intravaginally respectively with 1.57 mg of progesterone;

FIGURE 15 is a series of photomicrographs showing the surface epithelial morphology of baboon endometrium;

20 FIGURES 16A and 16B are recordings of the contractile activity of two female baboons one of which was treated with

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microparticles containing estradiol and the other of which was not treated with hormone-containing microparticles.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In its broadest terms the objective of the present invention is to provide microparticles containing at least one medicinal agent which when deposited in the vagina are transported by the natural transport mechanism across the cervix into at least the uterus and possibly the fallopian tubes where release of the medicinal agent occurs. In one aspect of the present invention the microparticle delivery is employed to convey various antibodies or antigens directly to the internal reproductive organs to obviate systemic introduction of antigens or antibodies for the treatment of the reproductive organs. Systemic introduction, in fact, cannot be used as a means for administering many antigens and antibodies into the body for treatment of the reproductive organs. In a second major aspect of the present invention a method is provided for the introduction of contraceptive agent containing microparticles into the vagina followed by transport of the same across the cervix into the uterus. The direct and local introduction of the contracep-

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5 tive agent has the advantage that substantially smaller dosages
of many types of contraceptive agents can be self-administered
to achieve virtually the same contraceptive effect achieved
with larger amounts of drug introduced systemically. While the
method of the present invention is effective for the delivery
10 of contraceptive agent containing microparticles under normal
circumstances in which a woman is regularly cycling, the present
method can be modified so that a woman who is not regularly
cycling can be regulated and at the same time the internal
15 organs can be rendered increasingly susceptible to transport of
the microparticles containing contraceptive agent across the
cervix into the uterus and fallopian tubes. The desired effect
can be accomplished by incorporating a menstrual cycle regula-
tory and cervical transport promoting hormone which is normally
an estrogen or progestin in the microparticles in addition to
the contraceptive agent.

20 There are two basic ways in which the role of antibodies
can be stimulated in the body to counteract the effects of
antigens. One technique is active immunization while the other
is passive immunization. In order to actively immunize a subject,

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the subject is administered an antigen to induce the formation of endogeneous antibodies. Normally, this technique requires up to two weeks before a sufficiently good level of antibody response is achieved. Because of the delay involved, the active immunization technique imposes limitations for the treatment of infectious diseases which have a short incubation time, for the treatment of a disease actively in progress and for reversing or modifying the effects of drugs, toxins, hormones, and enzymes. The second basic immunization technique is passive immunization whereby antibodies are administered in order to achieve temporary immune protection. Passive immunization has the advantage that the biological effects are immediate and can be effectively used in patients suffering from immunodeficiency diseases. Moreover, active immunization is not limited to the use of non-toxic antigens because animal species can be used as the source of the protective antibodies. Transport of the micro-particles is controlled by the cyclic changes in the endogenous ovarian steroid hormones, estradiol and progesterone. During the first 14 days of the menstrual cycle or the follicular or estrogenic phase of the cycle, the ovaries produce estradiol which has a stimulating effect on the cervical muscle contraction.

The frequency and amplitude of the cervical contractions during the follicular phase steadily increase from day zero to day 14 at which time ovulation occurs and the cycle enters the luteal phase or progestational phase when the ovaries begin to secrete progesterone. Progesterone has an inhibitory effect on the contractile activity of the cervix or alternatively a muscle relaxing effect on the cervix. The ovarian hormones also exhibit an opposing effect in the cells of the cervix in that estradiol causes an accumulation of secretory products in the cells of the cervix while progesterone promotes the release of these products in the cervical lumen. The interactions described are the mechanism by which changes in the viscosity of cervical fluid occur.

The fluid or mucous of the cervix is dynamic and is an aqueous type of hydrogel. The transport of microparticles as well as sperm is dependent upon the permeability of the cervical mucous to the microparticles as well as the propulsion provided by estrogen induced contractions of the cervix. The most appropriate time for transport of microparticles across the cervix occurs when the uterus exhibits maximum contractile activity and

cervical mucous permeability. Accordingly, the greatest rate of transport of sperm or microparticles through the cervix should occur between day 12 and day 16 of the menstrual cycle, although the actual day of ovulation may vary from four to six days in different individuals with some transport occurring in some persons before day 12 of the cycle. Normally, the cervix is not very receptive to transport during the first twelve days of the menstrual cycle as well as between days 16 and 28. Thus, in order to deliver microparticles containing antigen, antibody or contraceptive agent into the cervix, the microparticles in an appropriate dosage need only to be deposited in the vagina prior to day 16 of the cycle, preferably before day 12.

In a major embodiment of the present invention advantage can be taken of the fact that estrogen and progestin hormones have a transport stimulating effect on the internal organs. Thus, microparticles containing either an estrogen or progestin and medicinal agent or estrogen or progestin containing microparticles with microparticles containing a medicinal agent can be introduced into the vagina to regulate the menstrual cycle of a woman who is not cycling regularly or to stimulate the cervix

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to transport microparticles across the cervix into the uterus and fallopian tubes. The locally absorbed progestin or estrogen in a biologically effective amount induces the necessary secretory changes in the endometrium of the cervix and promotes the contractile activity of the cervix necessary for microparticle transport. Once transport activity has begun, the microparticles are conveyed across the cervix into the uterus. Both estrogen and progestin in proper amounts will stimulate transport. However, a progestin at too high a level of concentration will have an adverse effect on microparticle transport because the progestins have a muscle relaxing effect on the tissues of the cervix. However, the adverse effect of the administered progestin can be reversed by the administration of a sufficient concentration of an estrogen via estrogen containing microparticles such as estradiol which as discussed supra induces contractile activity of the tissues of the cervix. Normally, when estradiol is delivered locally by way of the microparticles, the amount of microparticles administered should be sufficient to deliver from 0.1 to 1 mg per day over a 7-14 day period. On the other hand, when progesterone is incorporated

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in the microparticles, the amount of microparticles administered should be sufficient to deliver from 0.5 to 2 mg per day over a 7-14 day period.

As alluded to above the microparticles of the present invention can provide the feasibility of locally administering a contraceptive agent, antigen or antibody to the cervix while simultaneously exogenously activating a menstrual cycle in a non-cycling woman by the administration of an appropriate ovarian hormone and stimulating the cervix for microparticle transport.

Hence, estrogen containing microparticles can be administered such that estradiol or a synthetic estrogen is released at the cervix for a fourteen day period thus duplicating the first half of the menstrual cycle. When transport of the microparticles occurs across the cervix, medicinal agent in the microparticles or in separate microparticles is delivered to the uterus. Fourteen days after administration of the estrogen containing microparticles, progesterone containing microparticles optionally containing antibody or antigen are then administered. Thus, the complete natural menstrual cycle can be duplicated while providing antibody or antigen protection. Of course, it is also

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within the scope of this invention to deliver microparticles containing estrogen or progestin into the cervix to regulate the cycle and thereafter administer antigen or antibody containing microparticles at the period of the cycle when the cervix is receptive to transport. In the artificially induced cycle maximum transport across the cervix is achieved between days 12 and 16. Since the cycle regulatory hormones are administered locally in the present technique, effective estradiol activity can be achieved at dosage rates between 0.01 and 0.07 mg per day, while effective progesterone activity can be attained at dosage rates of 0.04 to 0.14 mg per day. Estradiol and progesterone are the regulatory hormones of choice. However, it is evident that other well known synthetic estrogens and progestins can be employed as substitutes for estradiol and progesterone, respectively. Suitable estrogens include estrone, mestranol, ethinyl estradiol, 2-methoxyestrone, 2-hydroxyestrone and estriol. Suitable progestins include norethindrone, dimethisterone, ethynodiol diacetate, norethynodiol, norethindrone acetate and norgestrol. When the synthetic compounds are employed, the dose employed depends entirely upon the biological potency of the synthetic estrogen or progestin compound.

Microparticles containing a medicinal agent such as antibody, antigen or contraceptive agent and/or menstrual cycle regulating

hormone can be formed in a variety of configurations. In perhaps the simplest situation shown in FIGURES 1 and 6 microparticles of a monolithic structure are prepared in which the desired antigen or antibody 2 on the one hand, or contraceptive agent 21 and cycle regulatory hormone 22 on the other hand, is distributed throughout a matrix material 1 (or 23) which is biodegradable and biocompatible. Once the microparticles are deposited in the vagina they begin to slowly deteriorate thereby continuously releasing the desired drug to achieve the desired daily dosage of drug over a prolonged period of time from the time they are deposited in the vagina until well after the microparticles have been conveyed across the cervix and deposited in the uterus. When the microparticles contain a cycle regulatory hormone, continuous release of the hormone regulates the properties of the cervical mucous and the contractile activity of the cervix. Since the microparticles of this particular embodiment continually release their active constituents from the time of deposition in the vagina, it is evident that most convenient results are achieved if the microparticles are formed such that they have an effective lifetime close to the period of the menstrual cycle so that microparticles need only be

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administered once during the cycle. However, this is only a preferred embodiment because the microparticles can be administered as many times as desired to achieve contraceptive and cycle regulatory effects.

5 FIGURE 2 shows another embodiment of the microparticles of a monolithic structure wherein antigen or antibody 2 is incorporated within matrix material 1 which in turn is surrounded by an envelope 3 of a drug free matrix material. This type of microparticle configuration wherein the particles are of a size
10 such that they possess sperm surrogate activity, is desirable where release of drug is to be delayed for some period of time after deposition of the microparticles in the vagina. The delayed release of drug obtained by using the above microparticles, for instance, would allow sufficient time for the micro-
15 particles to be deposited in the vagina, transported across the cervix and deposited in the uterus before the microparticles deteriorate to the point where the outer wall is essentially eliminated and drug release commences.

20 FIGURE 7 shows microparticles in which a core 25 of contraceptive agent 21 and cycle regulatory hormone

22 is encapsulated in a shell 27 of matrix material 24. This particular configuration of microparticles would be desirable where it is necessary to delay release of the active constituents of the deposited microparticles as described above
5 for the microparticles of FIGURE 2.

In still another microparticle configuration as shown in FIGURE 3, the microparticles can be designed for the sudden release of a large amount of antibody or antigen. To achieve this purpose the microparticles can be formed such
10 that a core 5 of antigen or antibody is encapsulated in a shell matrix material 1. Microparticles containing a core of drug would be particularly well suited in situations where an endogenous factor for disrupting the outer shell of the microparticles is exploited. For example, the difference in
15 pH of the mucosal fluids in the vagina on the one hand, and the cervix and uterus on the other hand, can be exploited such that deterioration of the outer shell occurs when the microparticles reach the area of the cervix or uterus. In this situation, the acidic pH of the vagina would have
20 little or no effect on the shell of the microparticles. However, when the microparticles are conveyed into the

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cervix where they are exposed to the neutral pH therein, breakdown of the outer shell would commence eventually resulting in the sudden release of drug which is advantageous where it is desirable to deliver a substantial amount of antibody to a patient suffering from an acute infection or having a high concentration of toxin. This procedure would be particularly desirable where it is desired to administer a booster response after an individual has already received a primary immunization.

10 In the treatment of patients for some disorders it is advantageous to be able to administer antigen or antibody in an intermittent fashion. This could be accomplished by the use of microparticles having the configuration shown in FIGURE 4 where alternate layers of drug alone or dispersed in matrix material 7 and drug free matrix material 1 are formed in concentric layers. When such microparticles are deposited in the vagina, release of drug does not occur until the outer layer of the microparticles disintegrates. Once the underlying layer is exposed drug release starts and continues until the layer disintegrates or releases the drug. Drug release ceases as the next underlying drug free layer is reached. In this manner intermittent release of the drug is achieved. An example of the

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applicability of this technique can be found in active immunization where the outermost drug layer releases antigen for a sustained period which is followed by a period for instance of a week or two, in which no drug is released. After the non-
5 drug containing layer disintegrates, a second period of antigen release starts. In this manner one could in a single administration of microparticles provide a primary immunization dose followed by a booster dose.

When it is desired to not only convey an antigen or antibody to the uterus through the cervix but also administer cycle
10 regulatory hormone in order to activate or regulate the natural transport mechanism, it is possible to administer microparticles of a monolithic structure as shown in FIGURE 1 in which both antigen or antibody and cycle regulating hormone are dispersed.
15 through a matrix material. In this manner, once the microparticles are deposited in the vagina, release of both hormone and antigen or antibody starts and eventually the microparticles are conveyed across the cervix into the uterus. A perhaps more selective regimen of administration could be provided by micro-
20 particles which have an outermost matrix layer containing cycle

regulatory hormone and an inner core of matrix material containing antigen or antibody. When such microparticles are administered, the sustained release of cycle regulatory hormone occurs, and when the cervix is receptive to transport, the microparticles are transported across the cervix into the uterus. Release of the antigen or antibody will occur in the cervix or uterus as the underlying antigen or antibody core of the microparticles is exposed. FIGURE 5 shows microparticles of the structure discussed above in which outer cycle regulatory hormone containing layer 9 encapsulates inner antigen or antibody containing core 11. The antigen or antibody alone can constitute the core of the microparticles or the antibody or antigen can be dispersed in the matrix material to form core 11. However, outer layer or shell 9 is formulated by dispersing a menstrual cycle regulatory hormone in a matrix material.

From the above discussion it is evident that antibody or antigen alone or in combination with a cycle regulatory hormone can be incorporated in microparticles in a variety of configurations depending upon how the drug or drugs are to be released. Moreover, while multi-layered microparticles such as the types shown in FIGURES 2, 4 and 5 are normally formed of a single type of matrix material, it is possible, if not desirable under

some circumstances, to formulate contiguous layers of the microparticles from different matrix materials. Still further, it is possible that under some circumstances, it may be desirable to deliver more than one antibody or antigen to the internal reproductive organs to treat more than one condition. Thus, for instance, monolithic microparticles could be prepared and delivered containing two different antibodies to passively treat two different diseases. In fact, it may be desirable under some circumstances to actively immunize a patient against one disorder and simultaneously passively immunize the patient against a second disorder with antigen or antibody delivered in the same microparticles. Of course, when more than one antigen and/or antibody is combined in one microparticle where they may be in contact and not in different layers of a microparticle, they must not react with each other.

Still another microparticle configuration is shown in FIGURE 8 wherein compatible, i.e. mutually non-reactive, contraceptive agent 21 and cycle regulatory hormone 22 are dispersed in matrix material 23 to form a core 25. The microparticles are completed by encapsulating the particles of drug containing

matrix material in a shell 27 of matrix material 24. The matrix material 23 and 24 of the inner core 25 and shell 27 can be the same material or different material. The use of different matrix materials is especially useful where it is desired to take advantage of the different rates of deterioration of the matrix materials or the different rates of diffusion of the drug through the matrix materials. Release of the contraceptive agent and cycle regulatory hormone does not occur until the shell of matrix material 24 has deteriorated.

FIGURE 9 shows a microparticle structure wherein a core 25 of contraceptive agent 21 in matrix material 23 is formed and then in turn core 25 is surrounded by a shell 27 of matrix material 25 containing cycle regulatory hormone 22. The microparticles of this particular configuration are especially useful where it is desired to deposit microparticles in the vagina to achieve the initial gradual release of only cycle regulatory hormone 22 which regulates the monthly cycle and stimulates transport of the microparticles across the cervix. In this manner regulation of the monthly cycle and at least initial transport of the microparticles can be initiated by the time the inner core 25 is sufficiently exposed to permit release of encapsulated contraceptive agent 21. Of course, the contraceptive

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agent can be encapsulated alone or dispersed throughout a core matrix material which can be the same as or different from shell matrix material 24.

5 A multiply layered microparticle configuration is shown in FIGURE 10. These microparticles possess an inner core 25 of a contraceptive agent 21 alone or dispersed in a matrix material 23. The core 25 is encapsulated in a shell 27 of a matrix material 24 which in turn is encapsulated in an outer shell 31 of matrix material 29 containing cycle regulatory hormone 28.

10 Microparticles of this particular configuration would be useful in those situations where it is desirable to administer cycle regulatory hormone after deposition of the microparticles in the vagina. After all of the cycle regulatory hormone has been released, release of the contraceptive agent would be delayed

15 until inner shell 27 has deteriorated to a sufficient extent to permit release of contraceptive agent from core 25. In the meantime, transport of the microparticles will occur thus achieving delayed release of the contraceptive agent until the bulk of the microparticles has been conveyed into the uterus.

20 With regard to the physical shape of the

microparticles, the microparticles can assume any possible shape ranging from ordered shapes such as spherical or oval to irregular shapes. The shape of the microparticles is not a factor in microparticle transport. Normally, the medicinal agent diffuses from the microparticles by gradual deterioration of the matrix material and/or by permeation of the agent from the matrix material.

The size of the microparticles is important insofar as the microparticles must possess sperm surrogate activity such that they can be conveyed by the natural transport mechanism of the reproductive organs upward from the cervix into the uterus and eventually into the fallopian tubes. If the microparticles are too large, they will cause contractions of the cervix which will expel the microparticles. Microparticles which are too small will not be conveyed upward into the internal reproductive organs. Usually, the microparticles range in size from 20 to 70 μm , preferably 20-60 μm .

The matrix material from which the microparticles are formed and in which the contraceptive agent and cycle regulatory hormone are dispersed is important not only from the viewpoint

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of sperm surrogate activity but also from the biocompatibility standpoint. In order for a material to be acceptable as a matrix material it should have no adverse effect on the internal female reproductive organs. The matrix material should also be
5 biocompatible in that it should not irritate the tissues of the cervix or uterus, it should not be carcinogenic and it should not induce inflammation in body tissues. The matrix material should be compatible with body tissues and it must be miscible with the cervical mucous. Another factor of importance is that
10 the matrix material must be biodegradable in that body chemical processes must be able to eventually breakdown the polymer so that it does not accumulate in the body. The matrix material should also have the ability, when in microparticle form, to slowly deteriorate over a period of time which at least
15 corresponds to the female monthly menstrual cycle. Suitable examples of polymer materials include polyglycolic acid, α , 1-poly-lactic acid, copolymers thereof, and the like. Other useful matrix materials include such materials as glycerol mono- and distearate. Other matrix materials include those which will
20 decompose in the neutral environment of the cervix.

In the preparation of the antibody or antigen containing microparticles essentially any known antigen or antibody can be

incorporated in the microparticles although those of particular use in the treatment of conditions and diseases of the internal reproductive organs are preferably used.

Suitable types of antigens which can be incorporated in the present microparticles include bacterial and viral pathogens of man and animals, however, enzymes and other biological factors involved in the reproductive process can also be used.

Suitable pathogenic antigens include Neisseria gonorrhea, Mycobacterium tuberculosis, Herpes virus (humonis, types 1 and 2), Candida albicans, Candida tropicalis, Trichomonas vaginalis, Haemophilus vaginalis, Group B streptococcus coli, Microplasma hominus, Hemophilus ducreyi, Granuloma inguinale, Lymphopathia venereum, Treponema pallidum, Brucella abortus, Brucella melitensis, Brucella suis, Brucella canis, Campylobacter fetus, Campylobacter fetus intestinalis, Leptospira pomona, Listeria monocytogenes, Brucella ovis, Equine herpes virus 1, Equine arteritis virus, IBR-IBP virus, BVD-MB virus, Chlamydia psittaci, Trichomonas foetus, Toxoplasma gondii, Escherichia coli, Actinobacillus equuli, Salmonella abortus ovis, Salmonella abortus equi, Pseudomonas aeruginosa, Corynebacterium equi, Corynebacterium pyogenes, Actinobacillus seminis, Mycoplasma bovigenitalium, Aspergillus fumigatus, Absidia ramosa, Trypanosoma equiperdum, Babesia caballi, Clostridium tetani.

Suitable examples of enzymes that may be involved in the reproductive process include ribonuclease, neuramidinase, trypsin, glycogen phosphorylase, sperm lactic dehydrogenase, sperm hyaluronidase, adenosinetriphosphatase, alkaline phosphatase, alkaline phosphatase esterase, amino peptidase, 5 trypsin chymotrypsin, amylase, muramidase, acrosomal proteinase, diesterase, glutamic acid dehydrogenase, succinic acid dehydrogenase, beta-glycophosphatase, lipase, ATP-ase alpha-peptate gamma-glutamylotrans peptidase, sterol-3-beta- 10 ol-dehydrogenase, DPN-di-aprorase.

Suitable examples of hormones acting as antigens include human chorionic gonadotrophin hormones, human placental lactogen, progesterone, estradiol and the like. Other antigens include those known as embryonic cellular 15 antigens which occur on the cellular surface of the trophoblast and are unique to the trophoblast. In addition to the above mentioned pathogens, mixtures of pathogens which can infect the female reproductive organs also can be incorporated in microparticles.

20 Examples of antibodies for passive immunization which can

be incorporated in microparticles include those which correspond to all of the above described antigens which are effective for active immunization. Antibodies which are effective against sperm, eggs, products of conception and the like can also be employed.

When the antigen or antibody containing microparticles are administered to a subject, they are administered in an amount such that the desired daily dosage level of antigen or antibody is delivered in an amount sufficient to elicit the desired response over the desired period of time, which for antigen would be about 0.5 to 1 mg of antigen per day over a 7-14 day period. The dosage range required for a booster immunization would vary from 0.5 to 1 mg per day over a 24 hour time span. With regard to passive immunization via antibody administration, the weight of antibody administered does not necessarily directly relate to the therapeutic effect realized. The important factor in terms of dosage for passive immunization is the titer of the antibody or the biological potency. The titer of an antibody refers to the maximum dilution of the antibody which elicits an effect in a test situation. Two different

preparations of antibody are not equally comparable on a weight basis because they have different biological potencies. An immunological titer of 1:500 is the minimum biological potency for any antibody to be administered by the process of the present invention. Moreover, the rate at which the immunoglobulin or antibody should be delivered to the cervix, uterus and fallopian tubes should not exceed 0.1 mg of antibody per day. Any dose rate less than this level which is effective in eliciting a therapeutic response is acceptable.

The antigen, antibody or contraceptive agent containing microparticles can be conveniently prepared by any well known procedure used in the past for the preparation of microparticles containing a pharmaceutical material. While the amount of antigen or antibody, and cycle regulatory hormone, if it is to be present, is not critical, normally, the microparticles contain from about 10 wt.% to 60 wt.% preferably 10 wt.% to 50 wt.%, most preferably 10 wt.% to 25 wt.% of antibody or antigen.

The primary limitation for the generation of passive immunization in a subject by the administration of antibodies in clinical medicine is that antibodies produced in animals quite often cause serum sickness or anaphylaxis when injected into

human recipients. However, the local delivery technique of the present invention circumvents this problem because not only are smaller dosages of antibodies required, but also systemic administration of antibodies is avoided.

5 In some instances active immunization is more advantageous than passive immunization such as for permanent protection against infectious diseases. Thus, when an antigen is delivered to the uterus and fallopian tube by the present technique, antibodies are secreted which not only provide the desired
10 immunological effect, but also are structurally and fundamentally unique from the type of antibody produced in response to systemic immunization. Systemic antibodies are not secreted by the reproductive organs, and it is for this reason that
15 systemic immunization is not an effective way of generating antibodies in the fluids of the cervix, uterus and fallopian tubes.

 Another aspect of active immunization pertains to fertility. In this case, sperm antigens are delivered by transport of antigen containing microcapsules into the cervix, uterus and fallo-
20 pian tubes. The antigen which is slowly released over a sustained period of time, stimulates the secretory tissues of the organs

to secrete protective antibodies in the fluid layer which coats the internal organs which essentially are the cervix, uterus and fallopian tubes. After copulation and deposition of sperm in the vagina, antibodies in the cervical mucous cause agglutination of the sperm in the cervix and prevent further transport of the sperm into the uterus. Antibodies against sperm also inactivate sperm by techniques other than agglutination.

For the contraceptive agent containing microparticles of the invention any type of contraceptive agent which has the desired contraceptive effect, especially in mammals, can be formulated in the present microparticles. Suitable examples of contraceptive agents include spermicidal compounds such as nonylphenoxypolyoxyethylene ethynol, Benzethonium chloride (benzyldimethyl [(2-(1, 1, 3,3-tetramethylbutyl-phenoxy) ethoxy) ethyl] ammonium chloride), Chlorindanol (7-chloro-4-indanol) and the like; and natural and synthetic hormones such as Progesterone (4-4-pregnene-3, 20-dione), Estradiol (estradiol 3, 17 β -dicyclonate), Norethindrone (17-hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one), Norgestrel (d, 1-13 β ethyl-17 α -ethynyl 17 β - hydroxy -4-en-3-one), Ethynodiol diacetate (3 β , 17 β -

diacetoxy-17 α -ethynyl-4-estrene), Lynestrenol (17 α -ethynylestr-4-en-17 β -ol), Medroxy-progesterone acetate (17 β -hydroxy-6 α -methylpregn-4-ene-3, 20-dione), Dimethisterone (17 β -hydroxy-6 α -methyl-17-1-propynyl-androst-4-en-3-one),

5 Megestrol acetate (17 α -hydroxy-6-methylpregn-4, 6-diene-3, 20 dione acetate), Chlormadinone acetate (6-chloro-17-hydroxy-pregna-4, 6-diene-3, 20-dione acetate), Ethinylestradiol (17 α -ethynyl-1,3,5(10)-estratriene 3 β -diol), Mestranol (3-methoxy-19-nor-17 α -pregna-1,3,5(10)-trien-20-yn-17-ol)

10 and the like. Another class of compounds within the scope of the present invention are those which induce early abortion in mammals. Suitable examples of compounds possessing abortifacient activity include antihistamines, cytotoxic drugs, ergot alkaloids, hormones, prostaglandins such as Prosta-

15 glandins E₂ and F₂ α (11 α , 15(S)-dihydroxy-9-keto-prosta-5-cis-13-trans-dienoic acid and 9 α , 11 α -15 (S)-trihydroxy-prosta-5-cis-13-trans dionoic acid, respectively), sympatholytic compounds, and the like. Of course, mixtures of various contraceptive agents where the individual compounds are bio-

20 logically compatible can also be used.

The amount of microparticles deposited in the vagina depends upon the amount of contraceptive agent that must be

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delivered to the uterus and fallopian tubes to achieve the desired contraceptive effect. In the case of hormones which produce a contraceptive effect, the dosage of hormone which should be administered ranges from 20 ug to 1000 ug per day.

5 In the case of spermicidal contraceptive agents it is not necessary to administer a daily dosage over most of the days of the menstrual cycle. It is only necessary to administer spermicidal agent for several days around midcycle when conception is possible at a dosage level sufficient to prevent conception. Normally, a dosage of 25 ug to 1000 ug per day for 7
10 days about midcycle will achieve the desired effect. Other types of contraceptive agents which can be used as discussed above include abortifacient drugs. These abortifacient drugs should be administered immediately following a missed menstrual
15 period for three to five days at a dose of 1 to 500 mg per day.

In the manufacture of the microparticles containing antigen or antibody and for a menstrual cycle regulatory hormone, any conventional method of forming the microparticles can be used. The selection of a particular method chiefly depends upon
20 the technical requirements of the matrix material and the

particular manner in which the microparticles are intended to be used. Generally, microencapsulation processes can be classified according to the three principal types, (1) phase-separation methods including aqueous and organic phase separation processes, melt dispersion and spray drying; (2) interfacial reactions including interfacial polymerization, in situ polymerization and chemical vapor depositions; and (3) physical methods, including fluidized-bed spray coating, multi- and single-orifice centrifugal coating, electrostatic coating and physical vapor deposition.

Microparticles containing medicinal or therapeutic agents can be delivered to the vagina by a variety of methods. The preferred method is to incorporate a fixed number of microparticles into a container designed for easy hand insertion into the vagina. The insertion container should be made of a biodegradable material that dissolves within minutes after placement in the vagina, thus, releasing the microparticles. Pharmaceutical type gelatin capsules can be conveniently used as a delivery system for the microparticles. The dose level can be varied by increasing or decreasing the number of microparticles in the delivery device.

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Of course, any number of other methods of variations, or this preferred method might be used. For example the microparticles could be molded into a solid vaginal suppository which affords the simplest most direct method of applying the microparticles by using an appropriate suspension medium such as gelatin. Creams, jellies, foams, or liquids might be used as a suspension medium for microparticles. Preparations of this type could be placed in the vagina using a loadable syringe or some type of pressurized vaginal inserter such as an aerosol device or a squeeze tube or bulb. A variety of different types of applicators for administering pharmaceutical agents to the vagina and rectum are in common use. A gelatin capsule is also a convenient vehicle for the delivery of microparticles.

Having now generally described the invention, a more complete understanding can be obtained by reference to certain specific examples which are included for purposes of illustration only and are not intended to be limiting unless otherwise specified.

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EXAMPLE 1

Preparation of Progesterone Containing
Polylactic acid Microcapsules

A 2.5 g amount of progesterone and 10.0 grams of
5 d,l-polylactic acid were dissolved in 38 grams of methylene
chloride. The resulting viscous solution was poured into a
250 ml kettle containing 120 ml of a 5 wt.% aqueous poly-
vinylalcohol solution. The dispersion obtained was stirred
at about 200 rpm until a stable emulsion had formed with the
10 droplets being in the range of 50 to 100 μ m in diameter. A
vacuum was applied to the emulsion until it began to foam and
then the rate of stirring was reduced to 600 rpm. After two
hours, most of the methylene chloride had evaporated. More-
over, continuous stirring was not required to prevent the
15 embryonic microcapsules from agglomerating. Thereafter, the
emulsion was centrifuged, the aqueous polyvinylalcohol
solution was decanted and the microcapsules were resuspended
in 150 ml of deionized water. For about 18 hours thereafter a
vacuum was continually applied to the stirred aqueous sus-
20 pension. Thereafter, the suspension was centrifuged and the
microcapsules obtained were washed with water and then col-
lected by vacuum filtration. The microcapsules were dried at
room temperature under a hard vacuum overnight, and then they

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were sieved whereby a fraction ranging between 43 and 61 μ m was obtained. By this procedure microcapsules containing 22 ± 1.5 wt.% progesterone were obtained.

EXAMPLE 2

5 Preparation of Progesterone Containing
 Glycerol Monostearate Microcapsules

A 1.0 gram amount of progesterone was added to 4 grams of molten glycerol monostearate and a portion of the molten mixture was poured into the reservoir of a melt sprayer and
10 heated to 167°C. The flow of nitrogen into the device to effect cooling was 60 liters per minute, while the flow of nitrogen into the sprayer to aerosolyze the molten mixture was adjusted to the maximum rate of 5.75 liters per minute. The aerosol was sprayed intermittently, and microcapsules
15 were collected and sieved, whereby a size fraction ranging between 43 and 61 μ m was collected. The microcapsules produced by this procedure were spherical and contained a 20 wt.% theoretical loading of progesterone.

EXAMPLE 3

20 Four female baboons were injected with d,l-polylactic

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microcapsules containing 7.87 mg of progesterone while five baboons were treated with d,l-polylactic microcapsules containing 7.87 mg of progesterone by the vaginal route of administration. All baboons were treated on day 5 and
5 uterine biopsies were taken on day 12. Daily blood levels of estradiol and progesterone were also obtained. The results of the daily determinations are shown in FIGURE 11 wherein FIGURE 11A shows the level of progesterone and estradiol for the intramuscular injection of microcapsules while FIGURE 11B
10 shows the levels of progesterone and estradiol for the vaginal administration of microcapsules. It is apparent that higher blood level concentrations of progesterone are found in the intramuscularly injected baboons than in vaginally treated baboons. There are two possibilities to account for
15 this: (1) not all of the microcapsules placed in the vagina remain in the body over the 7-day period of treatment; (2) not all progesterone released from the microcapsules following placement in the vagina reaches the bloodstream. Both of these possibilities probably contribute to the differences in
20 the systemic levels of progesterone between the two treatment groups. If systemic delivery of progesterone is considered

alone and the possibility of local delivery directly to the
uteris in the intravaginally treated animals is excluded, it
is logical to expect a more intense progestational effect
in baboons treated by injection than in those treated
5 vaginally. The results from dose-response experiments
support this expectation. Comparative histological examin-
ation of the endometrial biopsies of the baboons, however, do
not support this assumption. Histological examination re-
veals no significant reduction in the level of progesterone-
10 induced secretory activity in baboons treated by intravaginal
administration when compared to those treated by intra-
muscular injection. This is somewhat unexpected on the
basis of the difference in the systemic levels of progesterone.
This seemingly contradictory finding actually supports the
15 possibility for local delivery of progesterone in the
vaginally treated baboons. FIGURES 12a and 12b show the
histological appearance of the endometrium of a baboon
treated by the intravaginal administration of microcapsules
containing 7.87 mg of progesterone (H & F stained tissue at
20 20x and 100x magnification, respectively). FIGURES 12c and
12d represent the same tissue (PAS stained) at 20 x and 100x

magnification, respectively.

A second line of histological evidence which provides support for the local delivery of progesterone in the vaginally treated animals comes from the observation that
5 progesterone-induced alterations in endometrial histology are distributed evenly throughout the endometrium in baboons treated by injections; whereas, in baboons treated by intra-
vaginal deposition of the microcapsules, the effects are localized and vary from gland to gland with a notable
10 intensity of stimulation in the superficial glands under-
lining the surface epithelium (FIGURE 12). The absence of subnuclear vacuoles in the superficial glands in baboons treated by injection and the abundant presence of subnuclear
vacuoles in the superficial glands of baboons treated intra-
15 vaginally provides evidence of the local intrauterine delivery of progesterone in the intravaginally-treated baboons.

A comparative examination of the surface epithelial morphology by scanning electron microscopy provides further
20 evidence for localized progestational effects following intra-
vaginal treatment with the microcapsules. FIGURE 13 compares

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the morphology of the uterine epithelial surface of: normal non-treated day 12 baboon endometrium (FIGURE 13a); normal non-treated day 20 endometrium (FIGURE 13b); treated day 12 endometrium (intramuscular injection of microcapsules containing 7.87 mg of progesterone, FIGURE 13c); and treated day 12 endometrium (intravaginal deposition of microcapsules containing 7.87 mg of progesterone, FIGURE 13d).

Progesterone induces the formation of distinct microvillus projections on the luminal surface of the glandular epithelial cells. Microvilli are not normally present before ovulation (see day 12 control) but become quite conspicuous after ovulation (see day 20 control). Continuous progesterone treatment between days 5 and 12 induces the formation of numerous microvillus projections. Microvilli occur in an even distribution on the epithelial surfaces of baboons treated by injection. However, in baboons treated intravaginally the microvilli occur in distinct patches. The patchy uneven distribution of microcapsules occurs between areas in which the epithelial cells lack microvilli and other areas in which the microvilli vary in size. This uneven distribution of a progesterone-induced alteration in the morphology of the surface epithelium is indicative of localized areas of progesterone stimulation. Following systemic delivery,

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vaginally-treated baboons to resemble the pattern observed in normal non-treated controls. The rationale for this expectation is that the blood levels of both progesterone and estradiol in baboons treated by the intravaginal route with the low dose of microcapsules is identical to that which occurs normally.

Therefore, on the basis of endocrine data, there is little reason to expect hormone-induced alterations in the endometrial histology. The same rationale, however, does not hold for the animals treated by injection because following the treatment, detectable progesterone levels were found in the blood between days 5 and 12. Moreover, the estradiol levels appear to be somewhat depressed when compared to the normal controls. Again, the histological findings are contrary to the expected results. In spite of the lack of measurable systemic progesterone in baboons treated by the vaginal route, the endometrium exhibits distinct progestational effects.

Examination of the surface epithelial morphology by scanning electron microscopy reveals the frequent occurrence of microvilli providing clear evidence for progesterone stimulation as shown in FIGURE 15. In particular, FIGURES 15a and 15b

all areas of the endometrium receive a uniform dose of drug, whereas with local delivery, some areas may receive higher or lower doses depending on where the microcapsules are located within the uterus.

5 FIGURES 14A and 14B compare the mean progesterone and estradiol levels between baboons treated by either intramuscular injection (FIGURE 14A) or intravaginal administration (FIGURE 14B) with a dose of microcapsules containing 1.57 mg of progesterone under the conditions described above. This low dose of
10 microcapsules has a slight inhibiting effect on the estradiol levels when administered by injection and no effect when administered intravaginally. Exogenous progesterone is present in low levels in the blood between days 5 and 12 in baboons treated by injection. However, in baboons treated by the vaginal
15 route, exogenous progesterone could not be detected in the blood within the sensitivity range of the assay technique between days 5 and 12.

20 On the basis of the comparative hormone data shown in FIGURE 14 and excluding the possibility for local delivery, it seems logical to expect the histology of the endometrium of the

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are low magnification (9600) and high magnification (18240) micrographs of the surface epithelium of the treated baboon on day 12 of the menstrual cycle. FIGURE 15c is a micrograph of the epithelium which shows microcapsules containing progesterone on the surface of the epithelium while FIGURE 15d is a photomicrograph of the microcapsules themselves. Although the progesterone-induced alterations in the endometrial histology might occur in response to systemic progesterone that is too low to measure by the assaying system employed, a more likely explanation is that the progesterone-induced changes result from direct local intrauterine delivery of progesterone.

The most important point to emphasize is that with a low dose of microcapsules (i.e., 7.87 mg of progesterone) secretory changes were induced in the endometrium. Moreover, a dose response associated with the changes has been demonstrated suggesting that by increasing the dose it should be possible to achieve a level of effect sufficient to inhibit reproductive function.

FIGURES 16A and 16B compare the pattern of cervical muscle contractile activity between two baboons on the same day of the

menstrual cycle. A special transducer constructed as described by W. D. Blair and L. R. Beck in Ovum Transport and Fertility Regulation, 1976, pp. 41-74, Scriptor Publication (Copenhagen) placed in the cervix of each baboon was used to measure the pattern of the cervical contractions shown in the Figures. The transducer was connected to a strip chart recorder. FIGURE 16A shows the results obtained from a baboon treated by placing microparticles containing estradiol into the vagina while FIGURE 16B shows the results obtained from a control baboon untreated with microparticles. The results show that the treatment stimulates both the frequency and the amplitude of the cervical contractions. These contractions move the microparticles through the system.

Having now fully described the invention, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the invention as set forth herein.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. Antigen or antibody containing microparticles for the active or passive immunization of the internal female reproductive organs, which comprise:

microparticles containing an amount of antigen or antibody sufficient to elicit a response incorporated in a matrix material which is biocompatible and biologically degradable, said microparticles capable of being transported after deposition in the vagina by the natural mechanism of the internal female reproductive organs across the cervix into the uterus.

2. The microparticles of Claim 1, wherein said microparticles are of a size ranging from 20 to 70 μm and said matrix material is polylactic acid, polyglycolic acid, or copolymers of glycolic and lactic acids.

3. The microparticles of Claim 1, wherein said microparticles contain from 10 wt.% to 60 wt.% of said antigen or antibody.

4. The microparticles of Claim 1, Claim 2 or Claim 3, wherein said antigen is derived from a bacterial or viral pathogen and said antibody is one which responds to an antigen from a viral or bacterial pathogen.

5. The microparticles of Claim 1, Claim 2 or Claim 3, wherein said microparticles are formulated in a composition as a suppository, cream, jelly, foam or a liquid with a pharmaceutically acceptable excipient.

6. Antigen or antibody containing microparticles for the active or passive immunization of the internal female reproductive organs, which comprises:

microparticles of a particle size ranging from 20 to 70 μm containing an amount of antigen or antibody sufficient to elicit a response incorporated in a matrix material which is biocompatible and biodegradable, said microparticles capable of being transported after deposition in the vagina by the natural mechanism of the internal female reproductive organs across the cervix into the uterus.

7. The microparticles of Claim 1 wherein said matrix is selected from the group consisting of poly-d,l-lactic acid, polyglycolic acid, copolymers thereof and glycerol mono- or distearate.

8. The microparticles of Claim 6, wherein said microparticles contain from 10 wt.% to 60 wt.% of said antigen or antibody.

9. Microparticles containing contraceptive agent capable of being transported by the natural transport mechanism of the internal female reproductive organs into at least the uterus, which comprises:

a cycle regulatory hormone and contraceptive agent incorporated in a biocompatible and biodegradable matrix material as microparticles which possess sperm surrogate activity with the proviso that when said contraceptive agent is a hormone, the contraceptive hormone and cycle regulatory hormones are different, said cycle regulatory hormone being capable of stimulating said natural transport mechanism after said microparticles have been deposited in the vagina.

10. The microparticles of Claim 9, wherein said microparticles range in size from 20 to 70 μm and said biodegradable and biocompatible matrix material is a polymer selected from the group consisting of polyglycolic acid, polylactic acid, and mixtures thereof.

11. The microparticles of Claim 9 or Claim 10, wherein said transport inducing compound is an estrogen or a progestin.

12. The microparticles of Claim 9 or Claim 10, wherein said contraceptive agent is a hormone selected from the group consisting of progesterone, estradiol, norethindrone, norgestrel, ethynodiol diacetate, lynestrenol, medroxyprogesterone acetate, dimethisterone, megestrol acetate, chlormadinone acetate, ethinyl estradiol and mestranol.

13. Microparticles containing contraceptive agent capable of being transported by the natural transport mechanism of the internal female reproductive organs into at least the uterus, which comprises:

a cycle regulatory hormone and contraceptive agent incorporated in a biocompatible and biodegradable matrix material as microparticles of a particle size ranging from 20 to 70 μm which possess sperm surrogate activity with the proviso that when said contraceptive agent is a hormone, the contraceptive hormone and cycle regulatory hormones are different, said cycle regulatory hormone being capable of stimulating said natural transport mechanism after said microparticles have been deposited in the vagina.

14. The microparticles of Claim 13 wherein the matrix material is selected from the group consisting of poly-d,l-lactic acid, polyglycolic acid, copolymers thereof and glycerol mono- or distearate.

15. The microparticles of Claim 13 or Claim 14, wherein said contraceptive agent is a hormone selected from the group consisting of progesterone, estradiol, norethindrone, norgestrel, ethynodiol diacetate, lynestrenol, medroxyprogesterone acetate, dimethisterone, megestrol acetate, chlormadinone acetate, ethinyl estradiol and mestranol.

